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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 08/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/361,576	STOCKWELL ET AL.	
	Examiner	Art Unit	
	MY-CHAU T TRAN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-60,63-81 and 83-104* is/are pending in the application.

4a) Of the above claim(s) *84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-60, 63-81, 83, and 85-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 July 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/10/04 has been entered.

Status of Claims

2. Applicant's amendment filed 5/10/04 is acknowledged and entered. Claims 61-62 have been canceled. Claims 57-59, 63-65, and 81 have been amended.

3. Claim 82 was canceled. Claims 57-81 and 83-103 were amended, and Claim 104 was added by the amendment filed on 5/21/03.

4. Claims 1-56 were cancelled and Claims 57-103 were added by the amendment filed on 6/5/02.

5. Claims 57- 60, 63-81, and 83-104 are pending.

6. This application claims priority to three provisional applications. They are 60/094,305 filed 7/27/1998, 60/131,765 filed 4/30/1999, and 60/137,039 filed 6/1/1999.

Election/Restrictions

7. Applicant has elected the following species for the elected invention (Claims 57-104) in the reply filed on 10/15/02:

a. A species of ligand. Applicant elected antibody.

b. A species of second ligand. Applicant elected antibody.

c. A species of reagent. Applicant elected 5-bromodeoxyuridine.

d. A species of number of different cell line use. Applicant elected one.

8. Claim 84 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/15/02.

9. Claims 57-60, 63-81, 83, and 85-104 are treated on the merit in this Office Action.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 58-59, 63, 65, 71-81, 83, 85-104 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. (This is a written description rejection)

The instant claim 58 recites a method high-throughput method for screening test compound. The method comprises the steps of a) introducing into each of a plurality of reaction vessels: a plurality of cells, and one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated; b) introducing into each of the reaction vessels a first antibody characterized in that it associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process; c) assaying for association between the first antibody and the component in the reaction vessels; d) repeating step a; e) introducing into each of the reaction vessels a second antibody characterized in that it associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process; f) assaying for association between the second antibody and the component in the reaction vessels; g) optionally repeating steps d-f, wherein the second antibody is a third antibody; and h) retaining the information as a functional fingerprint. The plurality of reaction vessels comprises at least 96 reaction vessels.

The specification disclosure does not sufficiently teach the claimed method comprising the steps of d) thru g). The recited method steps d) thru g) of the instant claim 58 is interpreted as starting a new set of 96 reactions vessels with cells and test compounds for assaying with a different type of antibody such as the second antibody or third antibody, i.e. for each reiteration a "different" set of 96 reactions vessels are use to assay each different type of antibodies. The specification description is referring to a known transcriptional profiling methodology and

suggests modifying it (pg. 41, line 21 to pg. 42, line 14). The specification example 12 (see pg. 97, line 10 to pg. 98, line 7) is drawn to a cytoblot method of biological profiling wherein a master well plate of 6144, 1536, or 384 wells was created with each wells having different antibodies. A test plate of 6144, 1536, or 384 wells was seeded with cells and each well is treated with test compound. The cells were fixed and aliquots of the master antibody stocks were transferred to each well of the test plate during the cytoblot procedure. The antibodies were detected with a secondary antibody coupled to HRP and HRP retention on the cells is detected with luminol, hydrogen peroxide and the enhancer p-iodophenol. Thus a biological profile is produced. This method clearly does not provide an adequate representation regarding a method wherein each reiteration a "different" set of reactions vessels are use to assay each different type of antibodies. Thus the specification does not teach the claimed method of screening test compound with the recited method steps of d) thru g).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

With the exception of a cytoblot method of biological profiling in example 12 disclosed by the specification, the skilled artisan cannot envision the method of screening test compound wherein each reiteration a "different" set of reactions vessels are use to assay each different type of antibodies. Adequate written description requires more than a mere statement that it is part of

the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

In the present instance, the specification does not teach claimed method screening test compound wherein each reiteration a "different" set of reactions vessels are use to assay each different type of antibodies. Therefore, only the cytoblot method of biological profiling in example 12, but not the full breadth of the claim method meet the written description provision of 35 U.S.C 112, first paragraph.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 57-60, 63-81, 83, and 85-104 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) The phrase "the component" of claims 57 and 58 is insufficient antecedent basis for this limitation in the claim, i.e. does the phrase "the component" refers to the "biological component" or a different component such as the test compound.

b) The method step of "*retaining the information as a functional fingerprinting*" is vague and indefinite because it is unclear as to which "information" is being retain, i.e. the positive result of the assay is being retain or the negative result, or how it is being retain, i.e. is it being store in a database or in a chart.

c) The method step of "*retaining the information as a functional fingerprinting*" is vague and indefinite because it is unclear as what is the relationship of retaining information of the assay would produce a 'functional fingerprinting'.

d) Claim 73 is vague and indefinite because it is unclear how it further limit claim 72 since it appear to be a duplicate of claim 72.

14. Claims 57-60, 63-81, 83, and 85-104 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: The method of claims 57 and 58 are incomplete because it lacks the correlation step between the association of the antibody and the component with the test compound, i.e. how does the association of the antibody and the component relates to the test compound.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 57, 69, 71-72, and 88-90 are rejected under 35 U.S.C. 102(b) as being anticipated by Lam et al. (US Patent 5,510,240).

The instant claim 57 recites a high-throughput method for screening one or more test compounds to identify those that exert an effect on an intracellular biological or chemical process. The method comprises the steps of 1) introducing into each of a plurality of reaction vessels: a plurality of cells, and one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated; 2) introducing into each of the reaction vessels an antibody characterized in that it associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process; and 3) assaying for association between the antibody and the component in the reaction vessels. The plurality of reaction vessels comprises at least 96 reaction vessels.

Lam et al. disclose a library of bio-oligomers (refers to claims 88-89) (refers to the test compound of claim 57) and several methods for determining its biological activity (see e.g. Abstract; col. 4, lines 61-64; col. 5, lines 35-38; col. 17, lines 8-17). The bioactivity assay comprises adding to a 96 well plates the library of bio-oligomers that are attached to the bead, which will be release from the to test for bioactivity (refers to claim 90) (see e.g. col. 21, lines

46-50) and the cell (refers to step (1) of claim 57) (see e.g. col. 21, lines 58-61; col. 24, lines 59-45; col. 25, lines 11-21). The bioactivity is determined by a known MTT assay wherein MTT is added to each well of the bioassay plate (refers to step (2) of claim 57) and the product of the MTT metabolism is measured for optical density at 570 nm (refers to step (3) of claim 57 and claims 69, 71-72) (col. 25, line 57 to col. 26, line 10). Therefore the method of Lam et al. anticipates the presently claimed method of claim 57.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 57, 59-60, 63-71, 76-81, 83, and 85-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stylli et al. (US Patent 5,985,214) and Photiou et al. (*European Journal of Cancer*, **3/1997**, 33(3):463-470).

The instant claim 57 recites a high-throughput method for screening one or more test compounds to identify those that exert an effect on an intracellular biological or chemical process. The method comprises the steps of 1) introducing into each of a plurality of reaction vessels: a plurality of cells, and one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated; 2) introducing into each of the reaction vessels an antibody characterized in that it associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process; and 3) assaying for association between the antibody and the component in the reaction vessels. The plurality of reaction vessels comprises at least 96 reaction vessels.

Stylli et al. teaches an automated method and system for identifying chemicals having useful activity such as biological activities of chemicals and collecting informations resulting from such a process (e.g. see Abstract; col. 2, lines 35-41; col. 6, lines 1-24). The method comprise of testing a therapeutic chemical for modulating activity of a target in a cell-based assay (e.g. see col. 38, lines 46-67; col. 39, lines 1-9; col. 43, lines 6-9). The method comprises dispensing the reagents (compounds) into the addressable sample wells, which contains a predetermined volume of the sample (test cells) (e.g. see col. 6, lines 25-40; col. 8, lines 14-18). Additionally, Stylli et al. disclose the method of dispensing live cell cultures into the sample wells (e.g. see col. 59, lines 20-32). The wells include formats such as 96 wells, 384 wells, or

greater (e.g. see col. 15, lines 14-22). Stylli et al. disclose that various different cell-based assay can be employed with its systems wherein the assays include intracellular receptors (e.g. see col. 38, lines 46-47; col. 39, line 60 to col. 40, line 50; col. 42, line 10-15) and also various method of detection of the compound interaction with the target includes fluorescent measurement (e.g. see col. 27, lines 29-35; col. 28, lines 15-17; col. 39, lines 1-67 thru col. 42, lines 1-23). The compounds tested include combinatorial compounds (e.g. see col. 43, lines 21-44).

Furthermore, the features of remaining dependent claims, i.e. volume of the wells or wells format of claims 91-101 are either specifically described by the reference, or constitute obvious variations in parameters which are routinely modified in the art, and which have not been described as critical to the practice of the invention.

The cell-bases assay of Stylli et al. does not expressly include in the cell-base assay wherein the steps are introducing into the reaction vessels an antibody that is associated with a biological component and introducing a secondary ligand that binds specifically to the antibody.

Photiou et al. disclose a method for evaluating the in vitro antiproliferative activity (inhibiting cell replication and therefore DNA synthesis) of drugs as single agents and as combinations using human melanoma cell lines G361 and StMl11a (Abstract). Photiou et al. disclose an indirect immunofluorescence method in which cells are seeded on glass cover slips placed in 24-well plates, treated with drug(s), fixed, permeated, incubated with rabbit anti-tubulin antibodies, washed, and incubated with goat anti-rabbit antibody conjugated to FITC (secondary ligand) (e.g. see pg. 465, column 1). Photiou et al. discloses the interpretation of the tubulin immunofluorescence data, including the intracellular localization of the primary and

secondary antibodies (e.g. pg. 466, columns 1 and 2). The prevention of tubulin polymerization is a "post-translational event" and an "intracellular biochemical reaction."

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include in the cell-base assay wherein the steps are introducing into the reaction vessels an antibody that is associated with a biological component and introducing a secondary ligand that binds specifically to the antibody as taught by Photiou et al. in the method of Stylli et al. One of ordinary skill in the art would have been motivated to include in the cell-base assay wherein the steps are introducing into the reaction vessels an antibody that is associated with a biological component and introducing a secondary ligand that binds specifically to the antibody in the method of Stylli et al. since Stylli et al. disclose that any type of cell-base assay can be employed with system of Stylli et al. (e.g. see col. 38, lines 46-47; col. 39, line 60 to col. 40, line 50; col. 42, line 10-15). Thus any type of cell-base assay methodologies can be use in the system of Stylli et al. and the type of cell-base assay use would be a choice of experimental design and is considered within the purview of the cited prior art. Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the combination of Stylli et al. and Photiou et al. because Photiou et al. shown the success of the method for testing compounds for "intracellular biochemical reaction" (e.g. see fig. 1 on pg. 465).

20. Claims 72-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stylli et al. (US Patent 5,985,214) and Photiou et al. (*European Journal of Cancer*, **3/1997**, 33(3):463-470)

as applied to claims 57, 59-60, 63-71, 76-81, 83, and 85-104 above, and further in view of Walsh, (US Patent 5,990,092).

The instant claim 57 recites a high-throughput method for screening one or more test compounds to identify those that exert an effect on an intracellular biological or chemical process. The method comprises the steps of 1) introducing into each of a plurality of reaction vessels: a plurality of cells, and one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated; 2) introducing into each of the reaction vessels an antibody characterized in that it associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process; and 3) assaying for association between the antibody and the component in the reaction vessels. The plurality of reaction vessels comprises at least 96 reaction vessels.

Stylli et al. teaches an automated method and system for identifying chemicals having useful activity such as biological activities of chemicals and collecting informations resulting from such a process (e.g. see Abstract; col. 2, lines 35-41; col. 6, lines 1-24). The method comprise of testing a therapeutic chemical for modulating activity of a target in a cell-based assay (e.g. see col. 38, lines 46-67; col. 39, lines 1-9; col. 43, lines 6-9). The method comprises dispensing the reagents (compounds) into the addressable sample wells, which contains a predetermined volume of the sample (test cells) (e.g. see col. 6, lines 25-40; col. 8, lines 14-18). Additionally, Stylli et al. disclose the method of dispensing live cell cultures into the sample wells (e.g. see col. 59, lines 20-32). The wells include formats such as 96 wells, 384 wells, or greater (e.g. see col. 15, lines 14-22). Stylli et al. disclose that various different cell-based assay

can be employed with its systems wherein the assays include intracellular receptors (e.g. see col. 38, lines 46-47; col. 39, line 60 to col. 40, line 50; col. 42, line 10-15) and also various method of detection of the compound interaction with the target includes fluorescent measurement (e.g. see col. 27, lines 29-35; col. 28, lines 15-17; col. 39, lines 1-67 thru col. 42, lines 1-23). The compounds tested include combinatorial compounds (e.g. see col. 43, lines 21-44).

Furthermore, the features of remaining dependent claims, i.e. volume of the wells or wells format of claims 91-101 are either specifically described by the reference, or constitute obvious variations in parameters which are routinely modified in the art, and which have not been described as critical to the practice of the invention.

Photiou et al. disclose a method for evaluating the in vitro antiproliferative activity (inhibiting cell replication and therefore DNA synthesis) of drugs as single agents and as combinations using human melanoma cell lines G361 and StMl11a (abstract). Photiou et al. disclose an indirect immunofluorescence method in which cells are seeded on glass cover slips placed in 24-well plates, treated with drug(s), fixed, permeated, incubated with rabbit anti-tubulin antibodies, washed, and incubated with goat anti-rabbit antibody conjugated to FITC (secondary ligand) (e.g. see pg. 465, column 1). Photiou et al. discloses the interpretation of the tubulin immunofluorescence data, including the intracellular localization of the primary and secondary antibodies (e.g. pg. 466, columns 1 and 2). The prevention of tubulin polymerization is a "post-translational event" and an "intracellular biochemical reaction."

The method combination of Stylli et al. and Photiou et al. discloses a high-throughput screening method for test compounds that has an intracellular biological reaction, i.e. cell-base assay, wherein the method steps include introducing into the reaction vessels an antibody that is

associated with a biological component and introducing a secondary ligand that binds specifically to the antibody. However, neither of the Stylli et al. or Photiou et al. teaches a cell-base assay wherein 5-bromodeoxyuridine reagent is use as an indicator of intracellular biological reaction.

Walsh et al. discloses an in vitro assay for selecting GATA-6 molecules that modulate vascular smooth muscle proliferation (see example 4 of col. 28). The assay discloses that A7r5 cells (rat) are cultured in media containing the test molecule for up to 72 hours. The cells are harvested at various time points and the proliferative state of the cells is determined by immunohistochemical assays including a BrdU (refers to the claimed reagent of 5-bromodeoxyuridine) assay and a proliferating cell nuclear antigen (PCNA) assay, i.e. an assay for an intracellular antigen (see col. 28, lines 28-44). The assay further discloses that cells are fixed onto a tissue culture dish (reaction vessel), dried, and immunostained using a monoclonal antibody (see col. 28, lines 7-51). The assay discloses that the BrdU assay involves adding BrdU (a reagent known to exert an effect on the process of proliferation) to growth media (containing the cells to be tested) for 24 hours, fixing and permeabilizing the cells, and identifying proliferating cells with a mouse anti-BrdU antibody coupled to FITC (i.e. a second ligand coupled to a fluorescent tag) (col. 27, lines 13-25).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include a cell-base assay wherein 5-bromodeoxyuridine reagent is use as an indicator of intracellular biological reaction as taught by Walsh et al. in the method of Stylli et al. and Photiou et al. One of ordinary skill in the art would have been motivated to include a cell-base assay wherein 5-bromodeoxyuridine reagent is use as an indicator of intracellular

biological reaction in the method of Stylli et al. and Photiou et al. since Stylli et al. disclose that any type of cell-base assay can be employed with system of Stylli et al. (e.g. see col. 38, lines 46-47; col. 39, line 60 to col. 40, line 50; col. 42, line 10-15). Thus any type of cell-base assay methodologies can be use in the system of Stylli et al. and the type of cell-base assay use would be a choice of experimental design and is considered within the purview of the cited prior art. Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the combination of Stylli et al., Photiou et al., and Walsh et al. because Walsh et al. shown method of cell-base assay wherein 5-bromodeoxyuridine reagent is use as an indicator of intracellular biological reaction in example 4.

21. Claims 57-60, 63-71, 76-81, 83, and 85-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Photiou et al. (*European Journal of Cancer*, **3/1997**, 33(3):463-470) and Lam et al. (US Patent 5,510,240).

Photiou et al. disclose a method for evaluating the in vitro antiproliferative activity (inhibiting cell replication and therefore DNA synthesis) of drugs as single agents and as combinations using human melanoma cell lines G361 and StMl11a (Abstract). Photiou et al. disclose an indirect immunofluorescence method in which cells are seeded on glass cover slips placed in 24-well plates, treated with drug(s), fixed, permeated, incubated with rabbit anti-tubulin antibodies, washed, and incubated with goat anti-rabbit antibody conjugated to FITC (secondary ligand) (e.g. see pg. 465, column 1). Photiou et al. discloses the interpretation of the tubulin immunofluorescence data, including the intracellular localization of the primary and

secondary antibodies (e.g. pg. 466, columns 1 and 2). The prevention of tubulin polymerization is a "post-translational event" and an "intracellular biochemical reaction."

The method of Photiou et al. does not expressly disclose that the vessels use in method is 96 reactions vessels.

Lam et al. disclose a library of bio-oligomers (refers to claims 88-89) (refers to the test compound of claim 57) and several methods for determining its biological activity (see e.g. Abstract; col. 4, lines 61-64; col. 5, lines 35-38; col. 17, lines 8-17). The bioactivity assay comprises adding to a 96 well plates the library of bio-oligomers that are attached to the bead, which will be release from the to test for bioactivity (refers to claim 90) (see e.g. col. 21, lines 46-50) and the cell (refers to step (1) of claim 57) (see e.g. col. 21, lines 58-61; col. 24, lines 59-45; col. 25, lines 11-21). The bioactivity is determined by a known MTT assay wherein MTT is added to each well of the bioassay plate (refers to step (2) of claim 57) and the product of the MTT metabolism is measured for optical density at 570 nm (refers to step (3) of claim 57 and claims 69, 71-72) (col. 25, line 57 to col. 26, line 10).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include using 96 reactions vessels as taught by Lam et al. in the method of Photiou et al. One of ordinary skill in the art would have been motivated to include 96 reactions vessels in the method of Photiou et al. since the 96 wells plate, i.e. 96 reactions vessels, is a commonly use type of bioassay plate for bioassay. Thus the type of vessels use would be considered would be a choice of experimental design and is considered within the purview of the cited prior art. Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the method combination of Photiou et al. and Lam et al. because both disclose the

method of determining the biological activity of a compound (Lam: col. 4, lines 61-64; col. 5, lines 35-38; col. 17, lines 8-17; Photiou: Abstract).

Withdrawn Rejections

22. The rejections of claim 62 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter has been withdrawn in light of applicant's cancellation of claim 62.

23. The rejection of claims 57, 59-61, 64, 66, 67, 69, 71-74, 76-79, 81-83, 85-88, 102-103, and 104 under 35 USC 102(b) as being anticipated by Photiou et al. European Journal of Cancer 33(3):463-470 (March 1997) has been withdrawn in light of applicant's arguments see page 13, filed 5/10/04.

24. The rejection of claims 57-81, 83, and 85-104 under 35 USC 102(b) as being anticipated by Taylor (US Patent 6,103,479) has been withdrawn in light of applicant's arguments see pg. 14, filed 5/10/04.

25. The rejection of claims 89-101 under 35 USC 103(a) as being obvious over any one or more of Walsh, U.S. Patent 5,990,092 (November 1999); Photiou et al. European Journal of Cancer 33(3):463-470 (March 1997); Juan et al. Experimental Cell Research 239:104-110 (February 1988); Claycomb, U.S. Patent No. 6,316,207 B1 (November 2001) and the Final Conference Program of LabAutomation'98 held in San Diego, CA January 17-21, 1998, pages

99, 100, 124, 129, and 212 has been withdrawn in view of applicant's arguments, see pages 16-18, filed 5/10/04.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MY-CHAU T TRAN whose telephone number is 571-272-0810. The examiner can normally be reached on Mon.: 8:00-2:30; Tues.-Thurs.: 7:30-5:00; Fri.: 8:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANDREW WANG can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

mct
August 12, 2004

PADMASHRI PONNALURI
PRIMARY EXAMINER